Medical and Pediatric Oncology 30:240–248 (1998)

Risk Factors for Reduced Pulmonary Function After Malignant Lymphoma in Childhood

Karsten Nysom, MD,[1]* Kirsten Holm, MD,[2] Henrik Hertz, MD,[1] and Birger Hesse, MD[3]

The aim was to study pulmonary function after Hodgkin disease or non-Hodgkin lymphoma in childhood and to evaluate if younger age at diagnosis and therapy is a risk factor for reduced pulmonary function. We studied a population-based sample of survivors of Hodgkin disease (n = 22) or non-Hodgkin lymphoma (n = 19) in childhood. Pulmonary function test results were compared with reference values for our laboratory, generated by adjusting published reference values to fit 348 healthy never-smokers from a local population study. Data were analysed as standardised residuals, which are [observed minus predicted value] divided by the residual standard deviation of the reference equations. At a median of 11 years after diagnosis (range 2 to 24), the participants had significantly reduced lung volumes and transfer factor, unrelated to the few pulmonary symptoms. On average, the total lung capacity was reduced to −0.9 standardised residual and the transfer factor was reduced to −1.3 standardised residual. Young age at therapy seemed to be a risk factor for reduced lung function, especially when treatment included thoracic irradiation. No significant toxic synergism was observed between smoking and previous cancer therapy. Therapy without thoracic irradiation but with doxorubicin and cyclophosphamide was almost as toxic to lung function as therapy with thoracic irradiation but without doxorubicin and cyclophosphamide. This suggests a pulmonary toxicity of doxorubicin or cyclophosphamide. In conclusion, lung volumes and transfer factor were reduced several years after childhood Hodgkin disease or non-Hodgkin lymphoma, with young age at therapy as a risk factor, especially when combined with thoracic irradiation. Med. Pediatr. Oncol. 30:240–248, 1998.

Key words: Hodgkin disease; non-Hodgkin lymphoma; pulmonary function; late effects; risk factors for late effects; population-based study

INTRODUCTION

During the last three decades the survival rate after Hodgkin disease or non-Hodgkin lymphoma (NHL) in childhood has been considerably improved [1]. Consequently the frequency and severity of late effects in survivors of childhood Hodgkin disease and NHL have gained importance.

Most previous studies of pulmonary function after Hodgkin disease in childhood found a restrictive pulmonary deficiency [2–5]. However, one group found normal or better than normal lung function [6]. None of the studies identified any risk factors for reduced lung function. Pulmonary function after childhood NHL has only been studied in eight patients included in three series of survivors of various malignancies [3,4,7]. All previous studies of pulmonary function after childhood Hodgkin disease or NHL were hampered by few participants, lack of control groups, and, in some studies, a short follow-up.

The pulmonary function of adults treated for Hodgkin disease has been studied extensively, often with a long follow-up after therapy [8–14]. Most of these studies included patients diagnosed in childhood (i.e., before the age of 15 years), but the majority of participants were adults, and none of these studies paid any special attention to the pulmonary function of paediatric patients. The most frequent finding of these studies is a restrictive pulmonary deficiency after Hodgkin disease in adulthood, and several studies have furthermore identified risk factors for reduced lung function. Most of the risk factors were related to therapy, but the different studies identified several different and often conflicting risk factors.

Several late toxicities of cancer therapy are more pro-

[1]Section of Paediatric Haematology and Oncology, The Juliane Marie Centre, Rigshospitalet, Copenhagen, Denmark

[2]Section of Growth and Reproduction, The Juliane Marie Centre, Rigshopitalet, Copenhagen, Denmark

[3]Department of Clinical Physiology and Nuclear Medicine, The Centre for Medical Imaging and Engineering, Rigshospitalet, Copenhagen, Denmark

Contract grant sponsor: Agnes and Poul Friis Foundation; Contract grant sponsor: Jens Christensen and Wife Korna Christensen Foundation; Contract grant sponsor: Ib Henriksen Foundation.

*Correspondence to: Karsten Nysom, Section 4074, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen Ø, Denmark. E-mail: nysom@inet.uni2.dk

Received 15 January 1997; Accepted 18 November 1997

TABLE I. Characteristics of the Participants†

Characteristic	Chemotherapy + thoracic irradiation	Chemotherapy	All participants
Males/females	10/11	13/7	23/18
Diagnosis (with intrathoracic disease)			
Hodgkin disease	18 (13)*	4 (1)*	22 (14)
Non-Hodgkin lymphoma	3 (1)*	16 (6)*	19 (7)
Remission			
First	17	19	36
Second	4[a]	1	5[a]
Treated with splenectomy	9*	2*	11
Age at diagnosis	13.2 (3.9–15.0)	10.5 (4.2–14.1)	11.0
Age at completion of therapy	14.1 (5.9–22.5)	12.1 (5.1–16.8)	13.1
Age at follow-up	25.9* (12.2–38.1)	19.8* (10.6–34.3)	21.3
Follow-up from diagnosis	13.3* (2.9–23.7)	9.4* (2.3–21.3)	10.5
Follow-up from completion of therapy	11.3* (2.3–21.3)	7.2* (1.4–17.9)	8.5
Smokers	9	3	12

†Age and length of follow-up are given as median (range) in years.
[a]One patient was in third remission after salvage therapy including autologous bone marrow transplantation.
*$P < 0.05$ for difference between groups. All other differences between groups were not statistically significant.

nounced in children treated at a young age [15–18], but it is unknown whether younger age at diagnosis and treatment is a risk factor for reduced pulmonary function after treatment for Hodgkin disease or NHL in childhood.

We studied the pulmonary function of 41 survivors of childhood Hodgkin disease or NHL several years after treatment with chemotherapy but without allogeneic bone marrow transplantation. By studying a large, population-based cohort with a long follow-up after cessation of therapy, and by comparing our results with reference values based on several hundred local controls, we tried to avoid some of the drawbacks of previous studies.

MATERIALS AND METHODS

Patients

From the population-based Danish Cancer Registry [19], 47 cases of Hodgkin disease and 71 cases of NHL were identified. These patients were diagnosed between 1970 and 1992 (inclusive) when they were less than 15 years old and residing in East Denmark (population 2.3 million). On January 1, 1993, two patients with Hodgkin disease were still on therapy, while 13 patients with Hodgkin disease and 40 with NHL had died. None were lost to follow-up.

Twenty-four (75%) of the 32 eligible Hodgkin disease patients and 22 (71%) of the 31 eligible NHL patients gave their informed consent to participate in the present study. Two NHL patients were not invited to participate, one because she had been treated with surgery only, the other because of a database error. The other patients declined to participate for personal reasons. To reduce the number of confounding factors related to lung function, we excluded from the present analysis one patient treated with amiodarone after an acute myocardial infarction, one patient treated with allogeneic bone marrow transplantation including total body irradiation, and three patients treated with thoracic irradiation but no chemotherapy.

The remaining 41 participants were divided into two groups according to treatment: group TI consisting of 21 patients treated with chemotherapy and thoracic irradiation and group noTI consisting of 20 patients treated with chemotherapy but without thoracic irradiation. Some characteristics of the two groups are given in Table I.

Patients were treated with chemotherapy according to different protocols including either alkylating agents, anthracyclines, or both. Table II lists the doses of the drugs for which the two groups differed considerably, the doses of the two well-known lung toxic agents carmustine and bleomycin, and the doses of radiation. Seventeen patients received irradiation to fields other than the thorax.

At time of the study 10 participants were current smokers, 4 were ex-smokers, while 27 were never-smokers. Two ex-smokers had consumed only 0.045 and 0.25 pack-years of cigarettes 5 to 10 years before being studied (one pack-year is 20 cigarettes a day for 1 year). These 2 patients and the 27 never-smokers were considered non-smokers in the analysis. The other two ex-smokers had consumed 4.5 and 6.5 pack-years of cigarettes, and had stopped smoking 4 and 10 years before participating in the study. These two patients and the ten

TABLE II. Doses of Chemotherapy and Radiation*

	Chemotherapy + thoracic irradiation (n = 21)		Chemotherapy (n = 20)	
	Exposed	Median dose (range)	Exposed	Median dose (range)
Chemotherapy				
Bleomycin (mg/m^2)	3	115 (20–116)	3	113 (111–147)
Carmustine (mg/m^2)	4	231 (83–671)	5	702 (180–1,064)
Chlorambucil (g/m^2)	4	0.5 (0.5–2.6)	1	1.5
Cyclophosphamide intravenously (g/m^2)	2	7.2 and 7.8	14	7.1 (1.2–19.6)
Dacarbazine (g/m^2)	3	3.3 (0.8–4.5)	3	4.5 (4.4–5.6)
Doxorubicin (mg/m^2)	4	265 (50–446)	16	421 (113–528)
Lomustine (mg/m^2)	5	384 (67–525)	2	430 and 464
Methotrexate intrathecally (no. doses)	1	42	14	8 (4–26)
Methotexate perorally (g/m^2)	1	0.4	8	0.6 (0.3–1.2)
Methotrexate intravenously (g/m^2)	0		9	24 (1–80)
Mechlorethamine (mg/m^2)	9	53 (16–93)	1	12
Procarbazine (g/m^2)	18	6.9 (4.2–54.3)	3	8.2 (1.2–9.7)
Radiation fields				
Mantle	21	37 (37–40)[a]	0	
Inverted Y or abdominal	5	37 (20–40)	4	37 (26–40)
Central nervous system	1	24	5	24 (18–24)
Pharynx or cervical	2	8 and 21	2	40

*Chemotherapy doses are given cumulated per m^2 of body surface area; radiation doses are given in Gy.
[a]One patient received mediastinal irradiation only (40 Gy).

current smokers were considered smokers in the analysis, and had consumed a median of 5 pack-years of cigarettes (range 1 to 25) over a median period of 9 years (5 to 25).

Pulmonary Function Testing

All pulmonary function tests were performed in the same laboratory in accordance with the European recommendations [20] between October 1992 and May 1995. The forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) were measured with a pneumotachograph (Jaeger, Würzburg, Germany). Each measurement consisted of at least three maximal expiratory manoeuvres from total lung capacity (TLC) to residual volume with a variation of less than 5% in FEV_1 and FVC between the two best manoeuvres. The highest FEV_1 and FVC values were used, irrespective of the manoeuvre from which they derived. The ratio of FEV_1 to FVC (FEV_1/FVC) was calculated in percent. Flow-volume curves were evaluated by one of us (B.H.). The TLC was measured by the helium dilution technique (Jaeger) and the diffusion capacity for carbon monoxide with the single breath technique according to the recommendations given by the American Thoracic Society [21], except that TLC and diffusion capacity were only determined once if cooperation was good. The equipment detected carbon monoxide with an infrared spectrophotometer (Jaeger) and helium with a thermal conductivity method. All values were corrected to BTPS (body temperature, barometric pressure, and saturated with water vapour under these conditions). The equipment was calibrated at least once a day according to the guidelines of the manufacturer. This included volume calibration of the pneumotachograph with a manual calibration pump and an automated calibration sequence of the gas analyser.

Pulmonary function test results were compared with reference values for our laboratory, which were generated by adjusting published reference values [20,22,23] to fit 348 healthy 13- to 24-year-old Caucasian never-smokers from a local population study [24].

Data Analysis

To make data comparable, pulmonary function test results and heights were analysed as standardised residuals (observed value minus predicted value) divided by the residual standard deviation [20]. Standardised residuals are equivalent to standard deviation (Z-) scores. The distribution of pulmonary function test results and heights did not differ significantly from a normal distribution (Shapiro-Wilk test), so these results are given as mean values, 95% confidence intervals of mean, and ranges. All other data are reported as median values with

TABLE III. Pulmonary Function Test Results†

Variable	Chemotherapy + thoracic irradiation (n = 21)			Chemotherapy (n = 20)			All participants [mean (*P**)]
	Mean (95% CI)	Range	No. ↓/nl./↑[a]	Mean (95% CI)	Range	No. ↓/nl./↑[a]	
Forced vital capacity	−1.2 (−1.7 to −0.7)	−3.0 to 0.4	9/12/0	−0.9 (−1.3 to −0.5)	−2.5 to 0.8	2/18/0	−1.1 (0.3)
Forced expiratory volume in 1 second	−1.5 (−1.9 to −1.1)[b]	−3.1 to 0.3	10/10/0	−0.8 (−1.2 to −0.4)	−3.3 to 0.4	1/19/0	−1.1 (0.01)
FEV_1/FVC	−0.4 (−0.9 to 0.1)[b]	−2.5 to 1.3	3/17/0	0.3 (−0.1 to 0.8)	−2.1 to 1.7	1/18/1	0.0 (0.03)
Total lung capacity	−1.1 (−1.5 to −0.7)	−3.0 to 0.5	5/16/0	−0.8 (−1.2 to −0.3)	−2.7 to 1.1	3/17/0	−0.9 (0.3)
Transfer factor	−1.4 (−1.7 to −1.1)			−1.2 (−1.7 to −0.8)			−1.3 (0.5)
Non-smokers	−1.2 (−1.6 to −0.8)	−2.1 to −0.3	4/8/0	−1.2 (−1.7 to −0.7)	−2.6 to 0.9	6/11/0	−1.2 (0.9)
Smokers	−1.8 (−2.3 to −1.4)	−2.7 to −1.1	5/4/0	−1.4 (−3.3 to 0.4)	−2.2 to −0.6	1/2/0	−1.7 (0.4)
Flow-volume curve patterns	Restrictive: 9 Obstructive and restrictive: 2			Restrictive: 7			

†Results are given as standardised residuals; CI confidence interval.
[a]Number of participants with standardised residuals <−1.645/⩾−1.645 and ⩽1.645/>1.645.
[b]One participant had a missing value.
*Probability for difference between mean values of the group treated with thoracic irradiation and the group treated without thoracic irradiation (Student's *t*-test).

ranges. Student's *t*-test was used for determining whether height and pulmonary function test results differed significantly from the reference values (i.e., a standardised residual of 0), and for comparing the results of groups of patients. Pulmonary function test results were considered abnormal if they were more than 1.645 residual standard deviation from the predicted mean value [20]. If raised as well as reduced values of a variable are considered abnormal (TLC, FEV_1/FVC) this corresponds to two-sided 90% prediction limits for reference data. If only reduced values are considered abnormal (transfer factor, FVC, FEV_1) this corresponds to one-sided 95% limits. Multiple linear regression models were used to evaluate possible predictive variables of pulmonary function. The continuity adjusted Chi-square test and Mann-Whitney's unpaired test were used for comparing baseline characteristics between groups of patients [25]. Probabilities below 0.05 were considered statistically significant and data were analysed with the SAS computer software package (SAS Institute, Cary, NC).

Ethics

All patients and the parents of the children younger than 18 gave their written informed consent. The study was in accordance with the Helsinki II declaration and was approved by the local medical ethics committee of Copenhagen, Denmark (approval no. KF V92-097).

RESULTS

Participants

At follow-up the average height of the participants was not significantly different from national reference data [26] (mean standardised residual −0.1, 95% confidence interval −0.6 to 0.3, range −4.7 to 2.1). One participant used beclomethasone inhalations for asthma. Five participants complained of dyspnoea, two complained of cough at night, while four complained of cough on exertion. All other participants, including all smokers, were without pulmonary symptoms. Six participants (including 2 smokers) considered their physical work capacity better than that of other people their own age, 17 (4 smokers) considered it equal to that of other people their own age, 17 (5 smokers) considered it a bit inferior, and 1 smoker very inferior. Four participants had haemoglobin concentrations 0.1 to 0.3 mmol/l below the lower limits of normal of our laboratory. All others had values evenly distributed within the normal range of our laboratory (7–13 years: 7.5–9.7; females >13 years: 7.0–10.0; males >13 years: 8.0–11.0 mmol/l).

Lung Volumes

Pulmonary function test results (Table III) were not related to pulmonary symptoms or self-estimated physical work capacity (plots not shown). The mean FVC, FEV_1, and TLC were all significantly reduced compared with reference values (Table III), and 8 to 11 participants had reduced values, of whom 3 to 5 were smokers. The mean lung volumes were lower in group TI than in group noTI, but this was statistically significant only for FEV_1 (Table III). The tendency towards lower lung volumes in group TI compared with group noTI was also found when the analysis was restricted to the 29 non-smokers, and when the non-smoking NHL patient in group TI and the 3 non-smoking Hodgkin disease patients in group noTI were also excluded (data not shown).

FEV_1 to FVC Ratio and Flow-Volume Curves

The mean FEV_1/FVC standardised residual was 0.0 (Table III). Four participants (two of them smokers) had reduced values, and one smoker had a raised value. The mean FEV_1/FVC was significantly lower in group TI than in group noTI (Table III), also when only non-smokers were considered (data not shown). The flow-volume curves of 2 participants (both smokers) showed a combined obstructive-restrictive pattern, while 16 curves (4 from smokers) appeared restrictive. All other curves were normal. The patient who used beclomethasone inhalations for asthma had a normal flow-volume curve but a reduced FEV_1/FVC.

Transfer Factor

The mean transfer factor standardised residual was significantly reduced (Table III) and 16 participants had reduced values. The transfer factor tended to be lower in smokers than in non-smokers ($P = 0.07$), but the transfer factor of the 29 non-smokers was also significantly reduced (Table III).

The transfer factor values given were not corrected for haemoglobin concentration in the present study, because the reference values for pulmonary function for our laboratory were based on transfer factor measurements without haemoglobin correction and because the haemoglobin concentration of nearly all participants was within normal limits. Correcting the transfer factor to the average age-specific haemoglobin concentration of our laboratory according to the equation of Cotes [20] had no influence on conclusions concerning transfer factor (data not shown).

Relationship to Age at Diagnosis, Smoking, and Treatment Group

The relationship between pulmonary function and age at diagnosis was tested in multiple regression models predicting the pulmonary function from age at diagnosis, treatment group, and smoking state. Lung volumes (FVC, FEV_1, TLC), but not transfer factor or FEV_1/FVC, were significantly related to the age at diagnosis when controlled for treatment group and smoking state (regression coefficients +0.11 standardised residual/year, 95% confidence intervals 0.01 or 0.02 to 0.20). Compared with non-smokers, smokers had lower lung volumes (estimated difference 0.4 standardised residual) and transfer factor (estimated difference 0.6 standardised residual), but these relations were not statistically significant ($P = 0.08$–0.26). Patients from group TI had a transfer factor similar to that of group noTI (estimated difference 0.1 standardised residual, $P = 0.7$) but lower lung volumes and FEV_1/FVC (estimated difference in FEV_1 0.8 standardised residual, $P = 0.004$; estimated difference in other variables 0.4 to 0.7 standardised residual, $P = 0.06$–0.20). Patients from group TI had a proportion of restrictive flow-volume curve patterns similar to that of group noTI ($P = 0.4$), but the 21 participants who were younger at diagnosis had a significantly higher proportion of restrictive flow-volume curve patterns than the 20 participants who were older at diagnosis (13 of 21 vs. 5 of 20, $P = 0.04$). Pulmonary function test results were not significantly lower in patients treated with bleomycin or carmustine than in other patients when controlled for age at diagnosis, treatment group, and smoking state.

The analysis was then limited to the 29 non-smokers, for whom models predicting pulmonary function from treatment group and age at diagnosis were tested. Again lung volumes, but not transfer factor or FEV_1/FVC, were significantly related to the age at diagnosis (regression coefficients for FVC, FEV_1, and TLC +0.12, +0.14, and +0.14 standardised residual/year; 95% confidence intervals 0.01 to 0.23, 0.03 to 0.26, and 0.02 to 0.25), and again lung volumes and FEV_1/FVC, but not transfer factor, were lower in group TI than in group noTI. In Figure 1 lung volumes and FEV_1/FVC of the 29 non-smokers are plotted against age at diagnosis. The most important relationship between lung volumes and age at diagnosis seems to be lower lung volumes in patients from group TI who were treated at a young age.

The length of follow-up after diagnosis was significantly shorter for group noTI than for group TI. When only patients who were studied more than 7 years after diagnosis were considered (20 from group TI and 12 from group noTI), length of follow-up did not differ significantly ($P = 0.63$). Also in this subgroup lung volume standardised residuals were positively related to age at diagnosis when controlled for treatment group and smoking (regression coefficients for FVC, FEV_1, and TLC +0.14, +0.16, and +0.14 standardised residual/year, 95% confidence intervals −0.01 to 0.28, 0.02 to 0.29, and 0.01 to 0.27).

DISCUSSION

We found significantly reduced lung volumes and transfer factor and a high frequency of restrictive flow-volume curve patterns in 41 adolescents or young adults 2 to 24 years after diagnosis of Hodgkin disease or NHL. The reduced lung function was not related to the few pulmonary symptoms. Our study is the first to indicate that young age at therapy may be a risk factor for lung damage after treatment for childhood lymphoma, especially when treatment includes thoracic irradiation. Although not statistically significant in all models tested, the presence of a relationship between lung volumes and age at diagnosis was very consistent in the different models: lung volumes were approximately 0.1 standardised

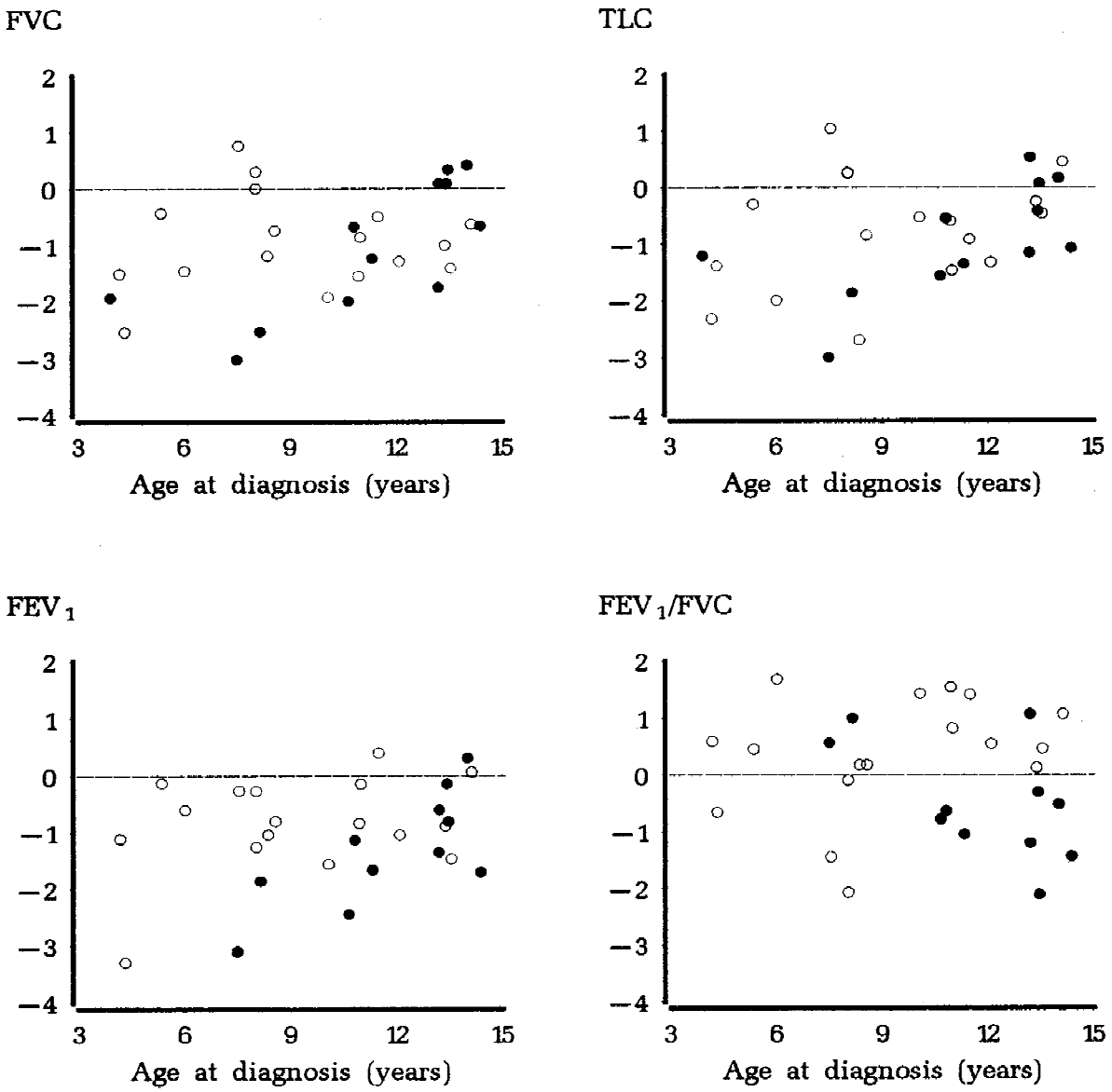

Fig. 1. Pulmonary function of 29 non-smoking survivors of childhood lymphoma. Standardised residuals ([observed minus predicted value] divided by the residual standard deviation) are plotted against age at diagnosis. Patients treated without thoracic irradiation (group noTI) are indicated as open circles, those treated with thoracic irradiation (group TI) as closed circles. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, ratio of forced expiratory volume in 1 second to forced vital capacity; TLC, total lung capacity.

residual higher per year of age at diagnosis. This corresponds to a difference of 1 standardised residual between a patient diagnosed at age 4 and one diagnosed at age 14, everything else kept equal.

As expected, but demonstrated here for the first time, smokers tended to have lower lung volumes and diffusion capacity than non-smokers after treatment for childhood lymphoma. Jensen et al. found that the diffusion capacity of patients with Hodgkin disease treated before they were 30 was reduced more than expected in smokers [27], but our estimates of the difference in lung volumes (approximately 0.4 standardised residual) and diffusion capacity (approximately 0.6 standardised residual) between smokers and non-smokers are comparable to data from large population studies [28]. Thus, the toxic effect of tobacco smoking on lung function did not seem bigger in our patients treated for childhood lymphoma than in a background population. However, due to the small number of participants the statistical power of our study is low. Negative results must therefore be interpreted with caution.

Lung function was almost equally reduced in group noTI and group TI. This is remarkable, since it is generally assumed that thoracic irradiation is more lung toxic than most types of chemotherapy. The reason why the difference is so small may be the differences in un-

derlying confounding factors between the two study groups, but several such confounders would also tend to cause a lower lung function in group TI than in group noTI: group TI comprised more smokers, more patients with intrathoracic disease, and more patients with Hodgkin disease and thus an assumed underlying immune deficiency, predisposing to pulmonary infections. If pulmonary function was still recovering slowly from damage decades after end of therapy, a longer follow-up of group TI could explain the very limited difference between the two groups, but when the analysis was limited to patients with a long and comparable follow-up period the difference was still small and the conclusions were essentially the same.

Another reason why the pulmonary impairment differed so little between the two groups could be that group noTI received a more lung toxic chemotherapy than group TI. Doxorubicin and intravenous cyclophosphamide were used more for group noTI than for group TI. That these two drugs are lung toxic would be in accordance with the study of Jenney et al. [29], in which cyclophosphamide and doxorubicin were risk factors for reduced lung volumes or transfer factor in a large group of childhood leukaemia survivors.

The almost identical pulmonary impairment in group TI and group noTI is interesting because the trend in the treatment of childhood lymphoma is to intensify chemotherapy while reducing radiotherapy, in order to reduce the late effects of radiotherapy. Although the present data suggest that this shift in therapy may not reduce pulmonary toxicity as much as expected, two recent reports point to another important reason for limiting the use of thoracic irradiation [30,31], namely the high incidence of second malignant neoplasms after childhood Hodgkin disease, in particular an extremely high risk of breast cancer in patients treated with thoracic irradiation.

Some participants received bleomycin or carmustine, known to be lung toxic. However, the number of patients exposed and the average doses were evenly distributed between group TI and group noTI (Table II), and lung function was not lower in the participants exposed to these drugs than in the others.

Mefferd et al. [2] found restrictive ($n = 6$) or obstructive ($n = 2$) pulmonary function abnormalities in 20 patients with paediatric Hodgkin disease 1 year after therapy with three cycles of MOPP (mechlorethamine, vincristine, procarbazine, prednisone), three cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), and irradiation to the involved field (15–25 Gy). Six of 11 patients tested had a reduced transfer factor. Restrictive lung disease [3,5] but normal transfer factor [3] were found in 7 and 12 survivors of Hodgkin disease, who had been treated 10–17 years earlier with chemotherapy, thoracic irradiation (35–40 Gy), or both. Huber et al. [4] found restrictive lung disease in four of 12 paediatric Hodgkin disease or NHL patients treated with mantle field irradiation (30–40 Gy), but in none of four patients treated with mediastinal irradiation. None of these studies identified any risk factors for abnormal pulmonary function after childhood Hodgkin disease. The reduced mean lung volumes and transfer factor of our participants are in accordance with the majority of these studies. However, it is difficult to compare our results with those of others, because all but one previous study [3] lacked an adequate control group for pulmonary function. One study even found most lung function parameters at, or above, predicted [6]. As it is unlikely that childhood cancer survivors have better lung function than controls, such a study is hard to believe.

Pulmonary function after childhood NHL has only been studied in eight patients included in groups of survivors of various malignancies [3,4,7]. One patient had restrictive pulmonary disease [4], five had normal lung function [3,4], whereas the lung function of the remaining two was not described separately [7]. Our results on NHL patients were in accordance with the few previous data.

Selection bias should not influence our results, since patients and controls were selected from population-based cohorts, and a high percentage of eligible subjects participated. It is a limitation of our study that the age range of participants was wider than that of controls, but the most important determinant of predicted lung function is height.

Several factors with a potential impact on the pulmonary function were related and could therefore not be analysed separately in our study: Hodgkin disease, intrathoracic disease, use of certain alkylating agents, thoracic irradiation, splenectomy, assumed underlying immune deficiency, and tobacco smoking. Similarly, the diagnosis of NHL and the use of doxorubicin, intravenous cyclophosphamide, and methotrexate were all closely interrelated (Tables I and II). Smoking and different treatments, however, seem most likely to explain the observed differences.

In the present study, pulmonary function tests before onset of the malignant disease were not available. Consequently, it was impossible to estimate how large a part of the observed pulmonary function abnormalities were caused by the malignant disease, the primary treatment, or any therapy for a relapse. Haematologic malignancies that are not in remission may themselves cause reduced pulmonary function [2]: at diagnosis the lungs may be infiltrated by malignant cells, or enlarged lymph nodes may compress the airways. The general condition of the patient is often considerably impaired due to causes such as anaemia, fatigue, acute infections, or pain, and this will often impair the effort of the patients at pulmonary function testing. Consequently, lung function measured at time of diagnosis will tend to be reduced compared

with the, usually unmeasured, lung function before onset of the malignant disease [32,33].

Our participants received chemotherapy according to numerous different protocols. Therefore, cumulative doses of individual drugs had to be used to characterise the treatments. Comparing radiation exposure is a complex matter because different radiation sources, fields, fractionation, and total doses were used [34,35]. For this reason patients were classified simply as irradiated to the thorax or not. The rather uniform cumulative doses of thoracic irradiation given made this approach more justified.

CONCLUSIONS

Pulmonary symptoms were few and mild, but lung volumes and diffusion capacity were significantly reduced 11 years after diagnosis of childhood Hodgkin disease or NHL. The pulmonary impairment seemed to be more severe in patients treated at a young age, especially when the treatment included thoracic irradiation. No significant toxic synergism was observed between smoking and cancer therapy. Therapy without thoracic irradiation was almost as toxic to lung function as regimens combining chemotherapy and thoracic irradiation. This suggests a pulmonary toxicity of doxorubicin or intravenous cyclophosphamide.

ACKNOWLEDGMENTS

We thank Vibeke Backer for having initiated a study of asthma, allergy, and bronchial hyperresponsiveness, from which normal controls were later identified, and Charlotte Suppli Ulrik for providing data on the pulmonary function of the normal controls. The study has received financial support from the Agnes and Poul Friis Foundation, the Jens Christensen and Wife Korna Christensen Foundation, and the Ib Henriksen Foundation.

REFERENCES

1. de Nully Brown P, Olsen JH, Hertz H, Carstensen B, Bautz A: Trends in survival after childhood cancer in Denmark, 1943–87: A population-based study. Acta Paediatr 84:316–324, 1995.
2. Mefferd JM, Donaldson SS, Link MP: Pediatric Hodgkin's disease: Pulmonary, cardiac, and thyroid function following combined modality therapy. Int J Radiat Oncol Biol Phys 16:679–685, 1989.
3. Makipernaa A, Heino M, Laitinen LA, Siimes MA: Lung function following treatment of malignant tumors with surgery, radiotherapy, or cyclophosphamide in childhood. A follow-up study after 11 to 27 years. Cancer 63:625–630, 1989.
4. Huber A, Gutjahr P, Kleinheisterkamp U: [Lung function following irradiation in pediatric cancer patients]. Dtsch Med Wochenschr 114:1367–1370, 1989 [in German].
5. Kadota RP, Burgert EO Jr, Driscoll DJ, Evans RG, Gilchrist GS: Cardiopulmonary function in long-term survivors of childhood Hodgkin's lymphoma: A pilot study. Mayo Clin Proc 63:362–367, 1988.
6. Ilhan I, Sarialioglu F, Bilgic H, Göcmen A, Büyükpamukcu M, Akyüz C, Kutluk T: Long-term pulmonary function in children with Hodgkin's disease. Acta Paediatr 85:324–326, 1996.
7. Leupold W, Ronisch P, Hahn B: [The effect of radio- and chemotherapy on lung function in children with malignant diseases] Zur Auswirkung von Strahlen- und Chemotherapie auf die Lungenfunktion bei Kindern mit malignen Erkrankungen. Pneumologie 44:1213–1216, 1990 [in German].
8. Shapiro SJ, Shapiro SD, Mill WB, Campbell EJ: Prospective study of long-term pulmonary manifestations of mantle irradiation. Int J Radiat Oncol Biol Phys 19:707–714, 1990.
9. Watchie J, Coleman CN, Raffin TA, Cox RS, Raubitschek AA, Fahey T, Hoppe RT, Van Kessel A: Minimal long-term cardiopulmonary dysfunction following treatment for Hodgkin's disease. Int J Radiat Oncol Biol Phys 13:517–524, 1987.
10. Smith LM, Mendenhall NP, Cicale MJ, Block ER, Carter RL, Million RR: Results of a prospective study evaluating the effects of mantle irradiation on pulmonary function. Int J Radiat Oncol Biol Phys 16:79–84, 1989.
11. Jensen BV, Carlsen NL, Groth S, Nissen NI: Late effects on pulmonary function of mantle-field irradiation, chemotherapy or combined modality therapy for Hodgkin's disease. Eur J Haematol 44:165–171, 1990.
12. Lund MB, Kongerud J, Nome O, Abrahamsen AF, Bjortuft O, Forfang K, Boe J: Lung function impairment in long-term survivors of Hodgkin's disease. Ann Oncol 6:495–501, 1995.
13. Hassink EA, Souren TS, Boersma LJ, Peerboom PF, Melkert R, van Zandwijk N, Lebesque JV, Bruning PF: Pulmonary morbidity 10–18 years after irradiation for Hodgkin's disease. Eur J Cancer 29A:343–347, 1993.
14. Gustavsson A, Eskilsson J, Landberg T, Larusdottir H, Svahn Tapper G, White T, Wollmer P: Long-term effects on pulmonary function of mantle radiotherapy in patients with Hodgkin's disease. Ann Oncol 3:455–461, 1992.
15. Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP: Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. N Engl J Med 324:808–815, 1991.
16. Shalet SM, Didi M, Ogilvy-Stuart AL, Schulga J, Donaldson MDC: Growth and endocrine function after bone marrow transplantation. Clin Endocrinol 42:333–339, 1995.
17. Jankovic M, Brouwers P, Valsecchi MG, Van Veldhuizen A, Huisman J, Kamphuis R, Kingma A, Mor W, Van Dongen Melman J, Ferronato L, et al.: Association of 1800 cGy cranial irradiation with intellectual function in children with acute lymphoblastic leukaemia. ISPACC. International Study Group on Psychosocial Aspects of Childhood Cancer [see Comments]. Lancet 344:224–227, 1994.
18. O'Driscoll BR, Kalra S, Gattamaneni HR, Woodcock AA: Late carmustine lung fibrosis. Age at treatment may influence severity and survival. Chest 107:1355–1357, 1995.
19. de Nully Brown P, Hertz H, Olsen JH, Yssing M, Scheibel E, Jensen OM: Incidence of childhood cancer in Denmark 1943–1984. Int J Epidemiol 18:546–555, 1989.
20. Quanjer PH, Tammeling GJ: Summary of recommendations. Standardized lung function testing, Report Working Party, European Community for Coal and Steel. Bull Eur Physiopathol Respir 19 (Suppl 5):7–10, 1983.
21. Single breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique. Statement of the American Thoracic Society. Am Rev Respir Dis 136:1299–1307, 1987.
22. Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G,

Cotes JE, Sanchis J, Paoletti P: Spirometric reference values for white European children and adolescents: Polgar revisited. Pediatr Pulmonol 19:135–142, 1995.
23. Rosenthal M, Cramer D, Bain SH, Denison D, Bush A, Warner JO: Lung function in white children aged 4 to 19 years: II. Single breath analysis and plethysmography. Thorax 48:803–808, 1993.
24. Nysom K, Ulrik CS, Hesse B, Dirksen A: Published models and local data can bridge the gap between reference values of lung function for children and adults. Eur Respir J 10:1591–1598, 1997.
25. Altman DG: ''Practical Statistics for Medical Research.'' London: Chapman and Hall, 1991.
26. Andersen E, Hutchings B, Jansen J, Nyholm M: Højde og vægt hos danske børn [Heights and weights of Danish children]. Ugeskr Laeger 144:1760–1765, 1982 [in Danish].
27. Jensen BV, Carlsen NL, Nissen NI: Influence of age and duration of follow-up on lung function after combined chemotherapy for Hodgkin's disease. Eur Respir J 3:1140–1145, 1990.
28. Knudson RJ, Kaltenborn WT, Burrows B: The effects of cigarette smoking and smoking cessation on the carbon monoxide diffusing capacity of the lung in asymptomatic subjects. Am Rev Respir Dis 140:645–651, 1989.
29. Jenney MEM, Faragher EB, Morris-Jones PH, Woodcock AA: Lung function and exercise capacity in survivors of childhood leukaemia. Med Pediatr Oncol 24:222–230, 1995.
30. Sankila R, Garwicz S, Olsen JH, Dollner H, Hertz H, Kreuger A, Langmark F, Lanning M, Moller T, Tulinius H: Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: A population-based cohort study in the five Nordic countries. Association of the Nordic Cancer Registries and the Nordic Society of Pediatric Hematology and Oncology. J Clin Oncol 14:1442–1446, 1996.
31. Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F, Meadows AT: Breast cancer and other second neoplasms after childhood hodgkin's disease [see Comments]. N Engl J Med 334:745–751, 1996.
32. Horning SJ, Adhikari A, Rizk N, Hoppe RT, Olshen RA: Effect of treatment for Hodgkin's disease on pulmonary function: Results of a prospective study. J Clin Oncol 12:297–305, 1994.
33. Cionini L, Pacini P, De Paola E, Corrado A, De Luca Cardillo C, Mungai V, Biti GP, Ponticelli P: Respiratory function tests after mantle irradiation in patients with Hodgkin's disease. Acta Radiol Oncol 23:401–409, 1984.
34. Dubray B, Henry Amar M, Meerwaldt JH, Noordijk EM, Dixon DO, Cosset JM, Thames HD: Radiation-induced lung damage after thoracic irradiation for Hodgkin's disease: The role of fractionation. Radiother Oncol 36:211–217, 1995.
35. Van Dyk J, Mah K, Keane TJ: Radiation-induced lung damage: Dose-time-fractionation considerations [see Comments]. Radiother Oncol 14:55–69, 1989.